**DRUG DISPOSITION**

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# Clinical Pharmacokinetics of Cisatracurium Besilate

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## Abstract

Cisatracurium besilate, one of the 10 stereoisomers that comprise atracurium besilate, is a nondepolarising neuromuscular blocking agent with an intermediate duration of action. Following a 5- to 10-sec intravenous bolus dose of cisatracurium besilate to healthy young adult surgical patients, elderly patients and patients with renal or hepatic failure, the concentration versus time profile of cisatracurium besilate is best characterised by a 2-compartment model. The volume of distribution (Vd) of cisatracurium besilate is small because of its relatively large molecular weight and high polarity.

Cisatracurium besilate undergoes Hofmann elimination, a process dependent on pH and temperature. Unlike atracurium besilate, cisatracurium besilate does not appear to be degraded directly by ester hydrolysis. Hofmann elimination, an organ independent elimination pathway, occurs in plasma and tissue, and is responsible for approximately 77% of the overall elimination of cisatracurium besilate.

The total body clearance (CL), steady-state Vd and elimination half-life of

cisatracurium besilate in patients with normal organ function are approximately 0.28 L/h/kg (4.7 ml/min/kg), 0.145 L/kg and 25 minutes, respectively. The magnitude of interpatient variability in the CL of cisatracurium besilate is low (16%), a finding consistent with the strict physiological control of the factors that effect the Hofmann elimination of cisatracurium besilate (i.e. temperature and pH). There is a unique relationship between plasma clearance and Vd because the primary elimination pathway for cisatracurium besilate is not dependent on organ function.

There are minor differences in the pharmacokinetics of cisatracurium besilate in various patient populations. These differences are not associated with clinically significant differences in the recovery profile of cisatracurium besilate, but may be associated with differences in the time to onset of neuromuscular block.

Cisatracurium besilate, one of 10 stereoisomers that comprise atracurium besilate, is a nondepolarising neuromuscular blocking agent (NMBA) with an intermediate duration of action (fig. 1). It is the *R-R′* optical isomer in the *cis-cis* configuration, and accounts for 14% of the atracurium besilate mixture.[1] Cisatracurium besilate is approximately 3 times more potent and has a similar neuromuscular blocking profile to atracurium besilate, although it has a slower onset (at equipotent doses).[2] However, the differences in onset are expected, based on the inverse relationship between potency and onset.[3,4] Cisatracurium besilate is not associated with dose-dependent histamine release at doses ranging from 0.1 to 0.4 mg/kg [2 to 8 times the effective dose ($ED_{95}$)].[5] A complete review of the pharmacology and clinical potential of cisatracurium besilate are presented elsewhere.[6]

## 1. Metabolism-Elimination

*In vitro* work in Sørensen buffer (pH 7.4, 37°C) and plasma (pH 7.39 to 7.42, 37°C) from 9 healthy volunteers suggests that cisatracurium besilate undergoes temperature- and pH-dependent Hofmann elimination to form laudanosine and a monoquaternary acrylate metabolite (fig. 2).[1] The monoquaternary acrylate then undergoes ester hydrolysis, via nonspecific plasma esterases, to form the monoquaternary alcohol metabolite and acrylic acid. In turn, the monoquaternary alcohol undergoes Hofmann elimination, at a much slower rate than cisatracurium besilate, to form a second molecule of laudanosine. The degradation rate of cisatracurium besilate in Sørensen buffer and plasma was similar in the presence or absence of a nonspecific plasma esterase.[1] However, the formation rate of the monoquaternary alcohol from

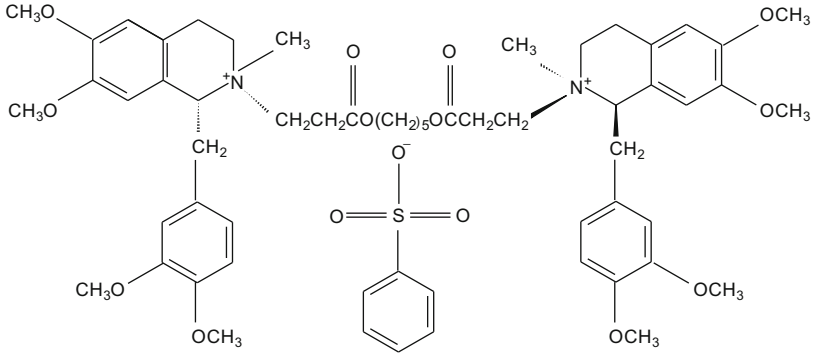


**Fig. 1.** Structural formula of cisatracurium besilate.

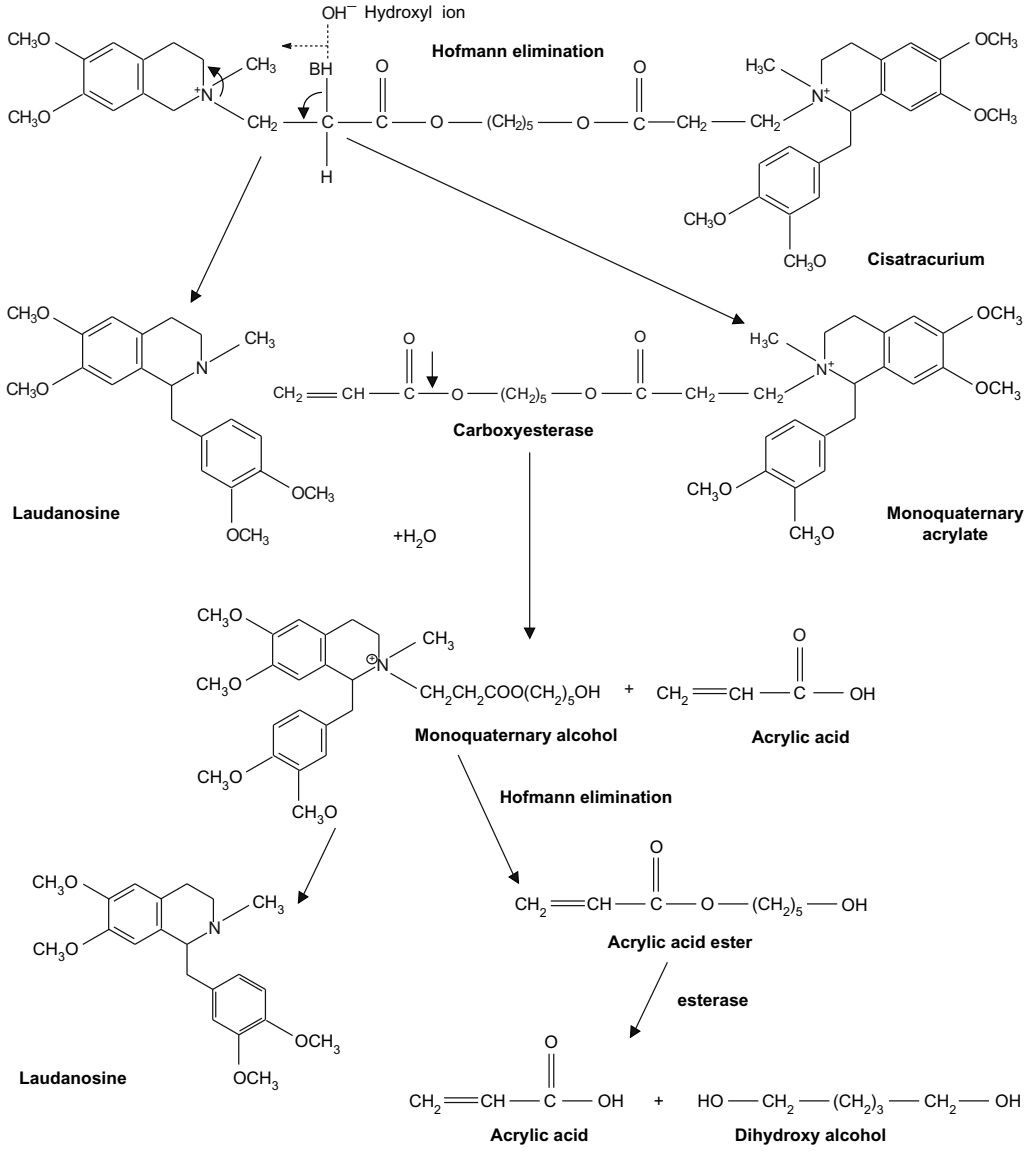


**Fig. 2.** Proposed metabolic elimination pathway for cisatracurium besilate in human plasma.[1]

the monoquaternary acrylate was significantly reduced by the addition of the nonspecific esterase,[1] suggesting that ester hydrolysis was not a metabolic pathway for the direct metabolism of cisatracurium besilate.

The results from this *in vitro* work are consistent with results from *in vivo* studies, which support the suggestion that Hofmann elimination, and not direct ester hydrolysis, is an important elimination pathway for cisatracurium besilate. In clinical studies, laudanosine and the monoquaternary alcohol metabolite, but not the monoquaternary acid metabolite, were detected in plasma and urine samples.[7-9] The mean *in vivo* elimination half-life ($t_{½\beta}$) of cisatracurium besilate in healthy adult surgical patients ranged from 22 to 30 minutes,[7-10]

similar to the *in vitro* half-life of 29 minutes.[1] In addition, following the administration of a 0.1 mg/kg dose of [$^{14}$C]cisatracurium besilate to 6 healthy male surgical patients, 95% of the dose was recovered in the urine, with less than 10% appearing as unchanged cisatracurium besilate. Most of the dose was excreted as conjugated desmethyl metabolites of laudanosine.[11] Finally, the magnitude of interpatient variability in total body clearance (CL) [as assessed using a population pharmacokinetic-pharmacodynamic model] was only 16%, a finding consistent with the strict physiological control of the factors that effect the Hofmann elimination of cisatracurium besilate.[12]

Therefore, *in vitro* and *in vivo* data suggest that the predominant pathway of cisatracurium besilate metabolism is Hofmann elimination to form laudanosine. Laudanosine is further metabolised to a number of conjugated metabolites which are excreted in the urine.

## 2. Pharmacokinetic Models

Following an intravenous bolus dose, plasma cisatracurium besilate concentrations decline over time in biexponential fashion, with the concentration-time data being best characterised by a 2-compartment model.[7-9] Because cisatracurium besilate undergoes Hofmann elimination in blood and tissues, a nontraditional 2-compartment model, with elimination from both compartments, is the most appropriate pharmacokinetic model (fig. 3). The rationale for this conclusion is as follows.

Nakashima and Benet[14] described exit site–dependent and –independent parameters for various pharmacokinetic models. CL is an exit site–independent parameter; therefore, values of CL obtained from either model (e.g. traditional, with elimination from the central compartment only, or nontraditional models) should be equivalent. However, the volume of distribution at steady state ($V_{ss}$) is dependent on the exit site(s) from the model. Hull[15] discussed the application of various models to describe the pharmacokinetics of atracurium besilate, explaining that either model could adequately describe the concentration-time curve. However, analysis using the traditional model, with elimination from the central compartment only, results in an underestimation of the $V_{ss}$. The magnitude of the underestimation of the $V_{ss}$ of cisatracurium besilate in healthy patients undergoing surgery was shown to be 17 to 20%.[9,13]

The nontraditional model was applied to plasma concentration-time data following cisatracurium besilate administration. Results from this modelling supported the idea that the major elimination pathway of cisatracurium besilate in healthy surgical patients was Hofmann elimination.[13] Approximately 77% of CL of cisatracurium besilate was accounted for by Hofmann elimination, while the remainder (23%), was accounted for by organ elimination pathways.[13] Similar findings were seen for patients with renal failure, where Hofmann elimination accounted for 88% of the clearance of cisatracurium besilate.[16]

These findings for cisatracurium besilate are in contrast to those found for atracurium besilate by Fisher et al.[17] The difference between atracurium

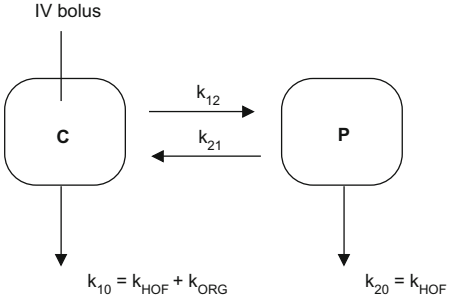


**Fig. 3.** Schematic of the nontraditional 2-compartment open model that most appropriately describes the pharmacokinetics of cisatracurium besilate. Elimination occurs from both the central (C) and peripheral (P) compartments. Hofmann elimination and organ-based elimination occurs from the central compartment. Only Hofmann elimination occurs from the peripheral compartment. **IV** = intravenous; $\mathbf{k_{12}}$ and $\mathbf{k_{21}}$ are the intercompartmental rate constants describing movement from the central compartment to the peripheral compartment and from the peripheral compartment to the central compartment, respectively; $\mathbf{k_{10}}$ = elimination rate constant from the central compartment; $\mathbf{k_{HOF}}$ = Hofmann elimination rate constant; $\mathbf{k_{ORG}}$ = organ elimination rate constant; $\mathbf{k_{20}}$ = elimination rate constant from the peripheral compartment (same as $k_{HOF}$) [from Kisor et al.,[13] with permission].

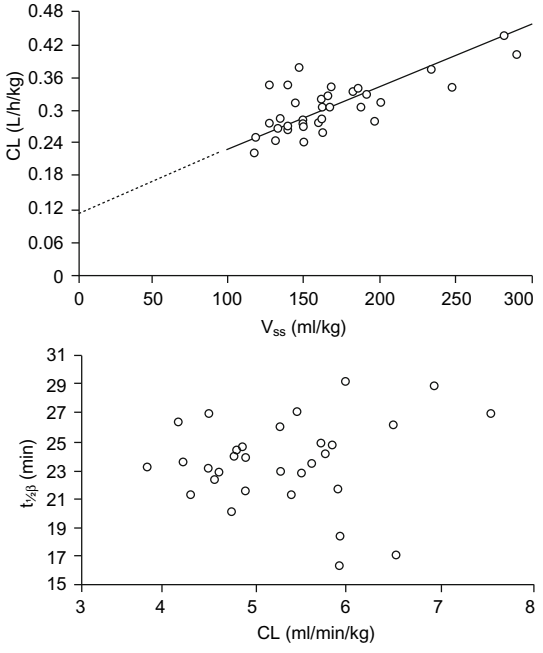


**Fig. 4.** Pharmacokinetic parameter relationships for cisatracurium besilate. **CL** = clearance; $t_{½\beta}$ = elimination half-life; $V_{ss}$ = steady-state volume of distribution. The dotted line in the top panel shows extrapolation to zero value on the *x*-axis (from Kisor et al.,[13] with permission).

besilate and cisatracurium besilate may be attributed to the fact that atracurium besilate contains 10 different isomers and the rate constants employed in the analysis by Fisher were composite values, whereas cisatracurium besilate is a single isomer represented by its own rate constant. However, and most importantly, the approach developed by Fisher et al.[17] allowed the contribution of Hofmann elimination to be determined for cisatracurium besilate and reaffirmed that, in humans, the elimination of cisatracurium besilate is minimally dependent on the liver and kidneys.[18]

## 3. Pharmacokinetic Parameter Relationships

Pharmacokinetic parameter relationships for cisatracurium besilate are unique because of its organ-independent elimination. These relationships (i.e. between CL and $V_{ss}$; $V_{ss}$ or CL and $t_{½\beta}$) can only be accurately determined by using the non-traditional model with elimination from the central and peripheral compartments.

For drugs that undergo organ-dependent elimination, the $t_{½\beta}$ is dependent on CL and $V_{ss}$, with CL and $V_{ss}$ being independent parameters. The organ-independent Hofmann elimination of cisatracurium besilate, because of tightly controlled temperature and pH, 'fixes' the elimination rate constant (and therefore $t_{½\beta}$); thus, the CL of cisatracurium besilate is dependent on the $V_{ss}$, and as $V_{ss}$ increases (or decreases) so does the CL (fig. 4).[13]

Protein binding could also explain these relationships. In reference to organ clearance of a low extraction drug (e.g. cisatracurium besilate), CL is dependent on intrinsic clearance ($CL_{int}$) and on the fraction of unbound drug in the blood or plasma ($f_u$):

$$CL_{total} = CL_{int} f_u$$

The $V_{ss}$ is also dependent on the $f_u$:

$$V_{ss} = V_b + V_t(f_u/f_{ut})$$

where $f_{ut}$ is the fraction of unbound drug in tissue, $V_b$ is the volume of blood and $V_t$ is the volume of tissue. Therefore, changes in $f_u$ would result in parallel changes in $V_{ss}$ and CL which would be recognised as a relationship between these parameters.[19] Studies of the pharmacokinetics of cisatracurium besilate require acidifying the blood samples to inhibit further *in vitro* degradation via Hofmann elimination, which results in protein precipitation and prevents evaluation of the protein binding of cisatracurium besilate. Therefore, proving these relationships are due to protein binding has been elusive.

When considering pharmacokinetic relationships, it is more likely that the organ-independent elimination of cisatracurium besilate dictates the relationships, with the $t_{½\beta}$ being the independent parameter. These theoretical arguments do come into play when interpreting pharmacokinetic estimates in certain populations. For instance, the $V_{ss}$, and hence, CL of cisatracurium besilate are in-

**Table I.** Cisatracurium besilate pharmacokinetic parameter estimates (mean ± SD) in healthy adult surgical patients with normal organ function

| n | Dose (mg/kg) | CL (L/h/kg) | $V_{ss}$ (L/kg) | $t_{½\beta}$ (min) | MRT (min) | Reference |
|---|---|---|---|---|---|---|
| 12 | 0.1 IV bolus | 0.28 ± 0.05 | 0.11 ± 0.01[a] | 21.5 ± 2.4 | NR | 7 |
| 15 | 0.1 IV bolus | 17.58 ± 0.59 (L • $h^{-1}$)[b] | $V_1$: 4.52 ± 2.81 (L)[a,b] | 30.0 ± 1.2[b] | NR | 20 |
| | | | $V_2$: 4.65 ± 2.39 (L)[a,b] | | | |
| 11 | 0.1 IV bolus | 0.34 ± 0.05 | 0.16 ± 0.02[a] | 23.5 ± 3.5 | NR | 8 |
| 8 | 0.075 IV bolus | 0.28 ± 0.03 | 0.12 ± 0.02[a] | NR | 26.5 ± 3.6 | 21 |
| 8 | 0.15 IV bolus | 0.28 ± 0.04 | 0.12 ± 0.01[a] | NR | 25.6 ± 2.6 | |
| 8 | 0.3 IV bolus | 0.28 ± 0.05 | 0.12 ± 0.03[a] | NR | 25.3 ± 2.5 | |
| 10 | 0.1 IV bolus | 0.32 ± 0.07[a] | 0.14 ± 0.03[a] | 22.4 ± 2.7[a] | NR | 9 |
| | | 0.31 ± 0.05[c] | 0.18 ± 0.05[c] | 24.8 ± 2.1[c] | | |
| | 0.2 IV bolus | 0.28 ± 0.04[a] | 0.12 ± 0.02[a] | 25.5 ± 4.1[a] | NR | |
| | | 0.28 ± 0.04[c] | 0.16 ± 0.04[c] | 25.0 ± 3.8[c] | | |
| 31 | 0.1 IV bolus | 19.14 (17.58-20.7)[d] | 9.7 (7.6-11.8) (L)[a,d] | 28.4 | NR | 10 |
| 7 | 0.1 infusion (5 min) | 0.22 ± 0.07 | 0.079 ± 0.011[a] | NR | 22.6 ± 3.6 | 22 |

a Parameter derived from noncompartmental or traditional 2-compartment model with elimination from only the central compartment.

b Population typical value and standard error.

c Parameter derived from nontraditional 2-compartment model with elimination from the central and peripheral compartments.

d Mean and 95% confidence interval.

**CL** = total body clearance; **IV** = intravenous; **MRT** = mean residence time; **n** = number of patients/participants; **NR** = parameter not reported; $\mathbf{t_{½\beta}}$ = terminal elimination half-life; $\mathbf{V_{ss}}$ = steady-state volume of distribution; $\mathbf{V_1}$ = volume of the central compartment of a traditional 2-compartment model; $\mathbf{V_2}$ = volume of the peripheral compartment of a traditional 2-compartment model.

creased in patients with end-stage liver disease (see below, section 6) as compared with relatively healthy patients undergoing surgery.[8] Therefore, when considering the elimination of cisatracurium besilate from the body, $t_{½\beta}$ is the independent parameter of interest.

## 4. Pharmacokinetics-Pharmacodynamics in Healthy Surgical Patients

### 4.1 General Pharmacokinetics

The pharmacokinetics of cisatracurium besilate were examined in adult patients with normal organ function (table I). Data from Eastwood et al.[20] and Ornstein et al.[7] were analysed using a 2-compartment model with elimination from the central compartment only. The clearance values were not affected by the fact that peripheral elimination was ignored; however, the $V_{ss}$ was an underestimate.

DeWolf et al.[8] and Bergeron et al.[23] described the pharmacokinetics of cisatracurium besilate using noncompartmental methods, which assumes elimination occurs from a central compartment only. As with the traditional model, the $V_{ss}$ is underestimated when using noncompartmental methods.

Lein et al.[9] applied the nontraditional 2-compartment model with elimination from both the central and peripheral compartments, and compared pharmacokinetic parameter estimates from this model to those derived from the model with elimination solely from the central compartment. The model with elimination from only the central compartment underestimated the $V_{ss}$ by 22 to 28% in healthy patients undergoing surgery. Combining data from the patients receiving cisatracurium besilate 0.1 mg/kg with data from 2 other studies, employing administration of the same dose in similar patients, Kisor et al.[13] showed the model with elimination from only the central compartment resulted in a 17% underestimation of the $V_{ss}$.

Sorooshian et al.[10] used nonlinear mixed effects modelling, a pharmacostatistical software program (NONMEM), to analyse cisatracurium

besilate concentration versus time data in young adult surgical patients (between 18 and 50 years of age) receiving a dose of twice the $ED_{95}$ (0.1 mg/kg). This analysis employed a model with elimination solely from the central compartment. These investigators then allowed elimination from the peripheral compartment (essentially using the non-traditional model) to determine the factor by which the $V_{ss}$ was underestimated. They found that the traditional model underestimated the $V_{ss}$ by a factor of 1.55, with the underestimation occurring entirely in the peripheral compartment.[10]

These studies neither utilised early rigorous sampling schemes as suggested by Ducharme et al.,[24] nor employed simultaneous sampling of arterial and venous blood,[25] which may have identified pharmacokinetic differences and better described the pharmacodynamics of cisatracurium besilate. Studies with atracurium besilate showed that the pharmacokinetics and pharmacokinetic-pharmacodynamic relationship for atracurium besilate were dependent on the sampling site.[25] The pharmacokinetic parameter estimates of cisatracurium besilate derived from arterial and venous sampling from patients in separate studies were similar; however, simultaneous sampling from an artery and vein within patients was not performed.[13]

Tran et al.[26] reported a CL of 0.22 ± 0.07 L/h/kg and a $V_{ss}$ of 0.08 ± 0.01 L/kg in healthy patients undergoing surgery receiving 0.2 mg/kg of cisatracurium besilate given as a short infusion. Pharmacokinetic parameters were estimated using noncompartmental methods and thus, the $V_{ss}$ was an underestimate.

The renal clearance of cisatracurium besilate in healthy patients undergoing surgery was calculated to be 16.4% of the total clearance; thus, renal elimination accounts for most of the non-Hofmann (organ) elimination of cisatracurium besilate.[13]

In addition to characterising the pharmacokinetics of cisatracurium besilate in individuals with normal organ function, the data showed that the pharmacokinetics of cisatracurium besilate were independent of dose for doses between 0.1 and 0.2 mg/kg,[9] between 0.075 and 0.3 mg/kg[23] and between 0.1 to 0.4 mg/kg.[27] These findings were not unexpected, as Hofmann elimination, being dependent on temperature and pH, would not be expected to be capacity limited.[13]

Overall, the concentration-time profiles for the same dose of cisatracurium besilate in patients with normal renal and hepatic function were very

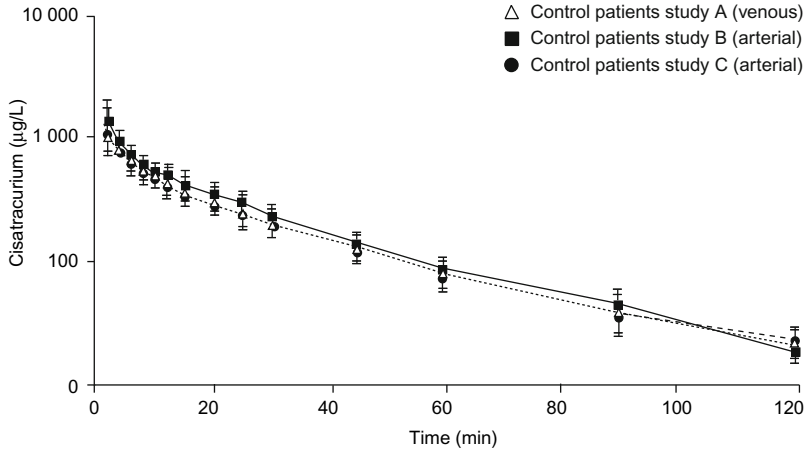


**Fig. 5.** Mean (± SD) concentration versus time data from 3 separate studies of cisatracurium besilate pharmacokinetics in adult patients with normal organ function (from Kisor et al.,[13] with permission).

reproducible (fig. 5). The strict physiological control of pH and temperature results in a low magnitude of patient variance in the clearance of cisatracurium besilate (16%).[12] The low variance of this compound has prompted investigators to use cisatracurium besilate as a model drug in examining new approaches to determining bioavailability.[28]

### 4.2 General Pharmacodynamics

In healthy adults receiving nitrous oxide/opioid/barbiturate anaesthesia, on a molar basis, cisatracurium besilate is 3.5 times more potent than atracurium besilate, with an $ED_{95}$ of 0.05 mg/kg.[2,22] With bolus doses of 3 and 4 times $ED_{95}$ (0.15 and 0.2 mg/kg, respectively), the mean time to 90% suppression (90% neuromuscular block) was 3.4 and 2.8 minutes, respectively.[29] As expected, the time to onset of neuromuscular block decreased as the dose of cisatracurium besilate increased.[2,21,22,29,30]

Also as would be expected, the clinically effective duration of neuromuscular block (the time from injection to 25% recovery of neuromuscular function) increased with increasing cisatracurium besilate dose in a predictable fashion.[2,22] At doses of 3 times $ED_{95}$ and 6 times $ED_{95}$, 0.15 mg/kg and 0.3 mg/kg, the duration of clinically effective neuromuscular blockade increased from 52 to 78 minutes.[30] The rate of recovery (e.g. 25 to 75% recovery index) from cisatracurium besilate–induced neuromuscular block was neither dependent on dose (2 to 8 times $ED_{95}$) nor factors such as age, renal failure, liver disease or prior suxamethonium chloride (succinylcholine chloride) administration.[7,8,10,31,32]

The rate constant describing equilibration between plasma cisatracurium besilate concentration and neuromuscular block ($k_{eo}$) ranged from 0.1 to 0.179 $min^{-1}$ in healthy adult surgical patients receiving a single bolus dose of cisatracurium besilate during opioid or inhalation anaesthesia.[8,11] In a parametric population pharmacokinetic-pharmacodynamic analysis, a $k_{eo}$ value of 0.058 $min^{-1}$ was estimated by combining data from healthy adult patients receiving single bolus doses of cisatracurium besilate with or without maintenance doses or infusions.[12] The differences noted were most likely caused by the limited number of $T_1$ suppression observations before maximum $T_1$ suppression and the collection of arterial *vs* venous blood. Because more onset and recovery data were included in the population analysis (e.g. time to 90% $T_1$ suppression, time to 25% $T_1$ recovery) the values obtained for $k_{eo}$ in the population analysis were more likely to be closer to the true value.

The most accurate value for $k_{eo}$ has been determined by administering a short duration infusion and collecting arterial plasma concentrations and $T_1$ suppression data both during and after the completion of the infusion.[33] An analysis using this method has recently been completed for cisatracurium besilate in healthy adult patients and resulted in a $k_{eo}$ value of 0.053 $min^{-1}$,[26] which was similar to the value obtained from the population analyses (0.058 $min^{-1}$).[12]

The concentration of the dose that produced 50% of the maximum effect ($EC_{50}$) for cisatracurium besilate ranged from 89 to 168 μg/L in patients receiving bolus doses of cisatracurium besilate during opioid or inhalational anaesthesia.[8,11] The $EC_{50}$ value estimate based on the parametric population pharmacokinetic-pharmacodynamic analyses was 141 μg/L.[12] Once again, when arterial samples were collected frequently following a short infusion of cisatracurium besilate, the $EC_{50}$ was estimated at 165 μg/L,[26] a value similar to those reported earlier.[12]

### 4.3 Factors Affecting the Pharmacokinetics-Pharmacodynamics in Healthy Surgical Patients

Population pharmacokinetic analyses were performed on data from healthy adult patients undergoing surgery.[12] The results showed that certain covariates were associated with statistically significant ($p < 0.01$) effects on CL or volume of the central compartment ($V_c$) of cisatracurium besilate. These covariates were not associated with clinically significant changes in the predicted recovery profile of cisatracurium besilate.[12] Slight differ-

ences in onset were predicted in some subsets, but warranted no changes in dosage recommendation.

The largest effects detected from the population pharmacokinetic analyses were associated with the use of inhalation anaesthesia. The use of inhalation anaesthesia was associated with a 78% larger $k_{eo}$, a 21% larger $V_{ss}$ and a 15% lower $EC_{50}$ for cisatracurium besilate.[12] These changes resulted in a slightly faster (≈45 sec) predicted time to onset in patients receiving cisatracurium besilate (0.1 mg/kg) during inhalation anaesthesia than in patients receiving opioid anaesthesia. However, there were no clinically significant differences in the predicted recovery profile of cisatracurium besilate for this subgroup.

This interaction, i.e. increased $k_{eo}$ and $V_{ss}$ in the presence of inhalational anaesthesia, is physiologically based (i.e. altered distribution due to changes in regional blood flow associated with the use of inhalation anaesthesia)[34] but does not affect dosage recommendations. Because patients in the present study[12] received cisatracurium besilate during stable anaesthesia while patients in the clinical setting received cisatracurium besilate closer to induction of anaesthesia, the faster onset predicted by the present model may or may not be clinically significant in general clinical practice.

Gender and the presence of obesity produced small changes in CL and/or $k_{eo}$. Adult female patients undergoing sugery had a 14% increase in $k_{eo}$ and obese patients had a 16% increase in $k_{eo}$ compared with nonobese patients. However, these effects were not associated with any clinically significant alterations in the predicted onset or recovery profile for cisatracurium besilate.[12,35]

In addition to describing patient characteristics altering the pharmacokinetics and pharmacodynamics of cisatracurium besilate in healthy patients undergoing surgery, the population pharmacokinetic analyses allowed for a better understanding of the variability in the time course of effects in healthy patients undergoing surgery which have been summarised in the product labelling.[35] Specifically, the magnitudes of interpatient variability in $k_{eo}$ and $EC_{50}$ (approximately 50 to 61%) were much higher than those observed for pharmacokinetic variables (CL and $V_c$; ≈16 to 27%), indicating that alterations in the time course of cisatracurium besilate-induced block are more likely because of variability in the pharmacodynamic parameters than in the pharmacokinetic parameters.

### 5. Pharmacokinetics-Pharmacodynamics in Elderly Patients

Table II presents pharmacokinetic parameter estimates for cisatracurium besilate from 2 separate pharmacokinetic studies performed in elderly patients. Ornstein et al.[7] administered 0.1 mg/kg of cisatracurium besilate as a bolus to 12 elderly patients (>65 years old) and 12 younger adult patients undergoing surgery (30 to 49 years old). The $V_{ss}$ of cisatracurium besilate was statistically significantly greater in the elderly patients as compared with the younger patient group ($0.13 \pm 0.02$ L/kg *vs* $0.11 \pm 0.01$ L/kg; $p = 0.008$). Because the $V_c$ was similar between the two groups, the difference in $V_{ss}$ was attributed to an increase in the volume of the peripheral compartment.[7] Sorooshian et al.[10] described similar results in a group of 33 elderly patients (>65 years of age) when compared with 31 younger patients. These studies showed that the $V_{ss}$ of cisatracurium besilate was 17 to 37% higher in elderly patients as compared with young adult patients. However, the values for $V_{ss}$ reported for these patients were most likely underestimates, as the models applied did not account for elimination from the peripheral compartment.

While the study by Ornstein et al.[7] identified a statistically significant increase in the half-life of cisatracurium besilate in the elderly, neither study showed a difference in the clearance between elderly and young adult patients. Interestingly, the relationships between the pharmacokinetic variables (e.g. CL and $V_{ss}$), as described earlier, were not seen in these studies. The reason for this is not clear.

The rate of equilibration between plasma cisatracurium besilate concentrations and neuromuscular block was reported to be slower in elderly patients compared with young adult patients.[10]

**Table II.** Cisatracurium besilate pharmacokinetic parameter estimates (mean ± SD) in specific patient populations

| Population | n | Dose (mg/kg) | CL (L/h/kg) | $V_{ss}$ (L/kg) | $t_{½β}$ (min) | Reference |
|---|---|---|---|---|---|---|
| Elderly | 12 | 0.1 IV bolus | 0.3 ± 0.05 | 0.13 ± 0.02[a] | 25.5 ± 3.7 | 7 |
| | 33 | 0.1 IV bolus | 19.14 (17.58–20.7) (L/h)[b] | 13.3 (9.9-16.7) (L)[a,b] | 36.3 | 10 |
| Renal disease | 17 | 0.1 IV bolus | 15.24 ± 0.73 (L/h)[c] | $V_1$: 4.52 ± 0.28 (L) $V_2$: 4.65 ± 0.24 (L)[a,c] | 34.2 ± 1.2[c] | 20 |
| End-stage liver disease | 13 | 0.1 IV bolus | 0.4 ± 0.07 | 0.2 ± 0.04[a] | 24.4 ± 2.9 | 8 |
| Intensive care unit patients | 6 | 0.19 (mg • $kg^{-1}$ • $h^{-1}$) constant infusion | 32.94 ± 4.74 (L/h)[d,e] | 21.9 ± 0.42 (L)[d,e] | 27.6 ± 3.6[d,e] | 36 |
| Pediatric | 20 | NR | 0.35 | $V_1$: 0.068 | NR | 37 |

a Parameter derived from noncompartmental or traditional 2-compartment model with elimination from only the central compartment.

b Mean and 95% confidence interval.

c Population typical value and standard error.

d Population mean and standard error of the mean.

e Parameter derived from a 1-compartment model.

**CL** = total body clearance; **n** = number of patients/participants; **IV** = intravenous; **NR** = not reported; **$V_{ss}$** = steady-state volume of distribution; **$t_{½β}$** = terminal elimination half-life; **$V_1$** = volume of the central compartment of a traditional 2-compartment model; **$V_2$** = volume of the peripheral compartment of a traditional 2-compartment model.

There were no differences in the sensitivity to cisatracurium besilate-induced neuromuscular block, as indicated by the $EC_{50}$.[10]

Overall, both studies indicated minor differences in the pharmacokinetics of cisatracurium besilate in elderly patients.[7,10] These differences were associated with a slightly slower time to onset (1 min), but no clinically significant differences in the recovery profile following cisatracurium besilate administration. Thus, dosage adjustment of cisatracurium besilate for use in the elderly patient is not required.

## 6. Pharmacokinetics in Patients with Renal or Hepatic Dysfunction

The pharmacokinetic parameter estimates for cisatracurium besilate in 17 patients with chronic renal failure were presented by Eastwood et al.[20] (table II). Using NONMEM, these investigators showed that the clearance of cisatracurium besilate was 13% lower in patients with renal failure as compared with healthy patients undergoing surgery, the Vd was similar between the 2 groups, and the $t_{½β}$ was approximately 4 minutes longer in patients with renal failure compared with healthy patients. When data from the same patients were analysed using noncompartmental methods, there were no statistically significant differences in CL, $V_{ss}$ or $t_{½}$ although the trends remained similar.[38]

The minor differences in the pharmacokinetics of cisatracurium besilate were associated with an approximately 1 minute slower time to onset in patients with renal failure compared with patients with normal renal function (3.7 *vs* 2.4 min, respectively).[31] The time to 25% $T_1$ recovery was similar between the 2 groups. However, the rate of recovery was slightly slower in patients with renal failure. Overall, there was more variability in the data in patients with renal failure than in patients with normal renal function.[31]

The population pharmacokinetic analyses in healthy adult patients[12] revealed that patients with mild to moderate renal dysfunction [creatinine clearance 1.68 to 4.2 L/h (28 to 70 ml/min)] had a 16% slower $k_{eo}$ than in patient with normal renal function.[12] This difference was associated with a slightly (≈40 sec) slower predicted time to onset following a bolus of cisatracurium besilate (0.1 mg/kg). However, there were no clinically significant differences in the predicted recovery profile of cisatracurium besilate for this subgroup. These results suggested that cisatracurium besilate dosage requirements were not altered in patients with renal dysfunction. However, because of the slower

onset of action, product labelling has recommended extending the interval between the administration of cisatracurium besilate and the intubation attempt in patients with mild to moderate renal dysfunction.[35]

A separate study was conducted in patients with liver disease undergoing liver transplantation and in healthy patients undergoing surgery with normal liver function. This study revealed that the $V_{ss}$ of cisatracurium besilate was larger and the CL of cisatracurium besilate was higher in liver transplant patients than in healthy patients undergoing surgery.[8] No difference was noted in the half-life between the groups. The renal clearance of cisatracurium besilate was 9% of the total clearance in the liver transplant patients (table II).[8]

The minor changes in pharmacokinetics were associated with a faster time to 90% $T_1$ suppression in patients undergoing liver transplant than in the control patients (2.4 *vs* 3.3 min, respectively).[8] The time to 25% $T_1$ recovery was approximately 7 minutes longer in patients undergoing liver transplant. The 25 to 75% recovery index was similar between the groups.[8]

Overall, there were minor differences in the pharmacokinetics of cisatracurium besilate in patients with renal or hepatic failure. These changes were associated with variations in the time to onset but were not associated with clinically significant changes in the recovery profile of cisatracurium besilate. No dosage adjustments are required for cisatracurium besilate in patients with organ failure.

## 7. Pharmacokinetics in Paediatrics

Population pharmacokinetic analyses were completed on data from 20 healthy paediatric patients undergoing surgery.[37] Each patient received cisatracurium besilate as a single dose with or without an infusion of cisatracurium besilate during halothane anaesthesia. The nontraditional 2-compartment model (with elimination from the central and peripheral compartments) with an effect compartment was fit to plasma cisatracurium besilate concentrations and neuromuscular block data. The CL and $V_c$ were similar to values reported for other populations (table II). The magnitudes of interindividual variability on CL were 12%.[37] The pharmacokinetics of cisatracurium besilate in healthy children undergoing surgery are similar to the values reported for healthy adults undergoing surgery.

The $k_{eo}$ and $EC_{50}$ were 0.133 $min^{-1}$ and 125 μg/L, respectively.[37] The magnitudes of interindividual variability in $EC_{50}$ were 25%.[37] The pharmacodynamics of cisatracurium besilate in healthy children undergoing surgery were similar to the values reported for healthy adults undergoing surgery, except for a larger $k_{eo}$ in paediatric patients. This larger $k_{eo}$ resulted in a more rapid time to onset and shorter duration of clinically effective neuromuscular block in children as compared with adults.[37,39-41]

## 8. Pharmacokinetics in Intensive Care Unit Patients

The pharmacokinetics of cisatracurium besilate were studied in 6 critically ill patients who required neuromuscular block to support mechanical ventilation.[36] The mean infusion time of cisatracurium besilate in these patients was 37.6 hours. The pharmacokinetic parameters were estimated using NONMEM, employing a 1-compartment model.[36] The Vd and CL of cisatracurium besilate in these patients were higher than reported for other populations (table II). However, the half-life was similar to that estimated in other populations. These findings were, not surprising on the basis of the relationship between CL and $V_{ss}$.

The rate of recovery from cisatracurium besilate-induced neuromuscular block (46 to 68 min) was consistent between patients following prolonged infusions in the intensive care unit (ICU).[42-44] Continuous infusion of cisatracurium besilate to adult patients in the ICU has not been associated with evidence of tolerance to the neuromuscular blocking effect of cisatracurium besilate.[36] However, there was one case report of a critically ill 7-month-old infant who required increased cisatracurium besilate doses (2.8 to 22.3

μg/kg/min) during a prolonged infusion of 6 weeks.[45]

## 9. Pharmacokinetics of Cisatracurium Besilate Metabolites

The metabolites of cisatracurium besilate include the monoquaternary alcohol, monoquaternary acrylate and laudanosine. The monoquaternary alcohol and monoquaternary acrylate metabolites are devoid of pharmacodynamic effects.[11] Laudanosine, which is also devoid of neuromuscular blocking effects, can cause transient hypotension, and at high doses in animals produces cerebral excitatory effects.[46-49] Since cisatracurium besilate is 3 times more potent than atracurium besilate, laudanosine concentrations following infusions of cisatracurium besilate may be lower than those following equipotent doses of atracurium besilate. In fact, this idea has been supported by data of Smith et al.[50] who reported laudanosine peak concentrations following cisatracurium besilate to be less than a third of those following atracurium besilate administration. Also, these investigators reported that the area under the concentration-time curve (corrected for differences in dose) for laudanosine were lower following cisatracurium besilate than following atracurium besilate.[50] Laudanosine concentrations were also lower in ICU patients receiving cisatracurium besilate undergoing mechanical ventilation as compared with those receiving atracurium besilate.[36]

Laudanosine, unlike cisatracurium besilate, is dependent on hepatic and renal function for its metabolism. In healthy patients undergoing surgery the $t_{1/2}$ ranged from 3.6 to 4.3 hours in patients receiving laudanosine 0.1 and 0.2 mg/kg, respectively.[9] As expected, the $t_{1/2}$ of laudanosine (following cisatracurium besilate administration), was prolonged in 2 patients with end-stage liver disease[8] because laudanosine is metabolised in the liver. Laudanosine concentrations were also higher in patients with renal failure as compared with surgical patients with normal renal function,[51] possibly because higher laudanosine concentrations may have resulted from the prolonged presence of the monoquaternary alcohol metabolite, which is a precursor to laudanosine (fig. 2). Regardless, the significantly higher laudanosine concentrations following cisatracurium besilate administration in patients with renal failure, as compared with healthy patients, were less than one-tenth of those reported following atracurium besilate administration in healthy patients undergoing surgery.[51] Therefore, laudanosine concentrations are lower following administration of cisatracurium besilate than after administration of atracurium besilate. This is as expected from the differences in potency between the 2 compounds.

## 10. Conclusions

Cisatracurium besilate is a nondepolarising NMB agent that undergoes Hofmann elimination, an organ independent elimination pathway, which occurs in plasma and tissue. This mechanism of elimination results in a low magnitude of interpatient variability in CL and a unique relationship between plasma clearance and Vd. There are minor differences in the pharmacokinetics of cisatracurium besilate in various patient populations. These differences are not associated with clinically significant differences in the recovery profile of cisatracurium besilate, but may be associated with differences in the time to onset.

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